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10/588,792	10/26/2006	Hiroyuki Kamiya	2006_1315A	9531

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EXAMINER	
PANDE, SUCHIRA	
ART UNIT	PAPER NUMBER
1637	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/588,792	KAMIYA ET AL.	
	Examiner	Art Unit	
	SUCHIRA PANDE	1637	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *04 June 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *12-22* is/are pending in the application.

4a) Of the above claim(s) *17-22* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *12-16* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claim Status

1. Amendment filed on June 4, 2008 is acknowledged. Applicant has amended base claim 12, withdrawn claims 17-22 and cancelled claims 1-11. Claims 12-16 are pending and will be examined in this action.

Response to Arguments

Re 112 rejection of claims 12-16

2. Amendment to claims 12-16 by using standard transitional phrase obviates the rejections under 112 raised in last office action. These rejections are accordingly withdrawn.

Re 103 rejection of claims 12-16 over Grunert et al.; Moriya and Marron et al.

Response to Arguments

3. Applicant's arguments filed June 4, 2008 have been fully considered but they are not persuasive. In addition, the amendment to base claim 12 has necessitated new ground(s) of rejection.

Applicant has amended the base claim to add a limitation that is taught by the cited art. Examiner would like to point out that the claim is written using open language "comprising" therefore the recited method can contain additional elements.

Grunert et al. teaches single stranded DNA obtained by denaturing PCR products. Since PCR products contain both the + and – strand therefore this single stranded DNA inherently contains single stranded DNA fragment homologous with either a sense strand or an antisense strand of the target DNA. Therefore the cited art

is still applicable to the amended claim. Hence the previously cited rejections are being maintained.

On page 5 Applicant is arguing limitations that are not recited in the instant claims, hence they are not being considered further.

NEW GROUNDS OF REJECTION NECESSITATED BY AMENDMENT

Claim Rejections - 35 USC § 112

4. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claims 12-16 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for in vitro homologous recombination of cells, does not reasonably provide enablement for in vivo homologus recombination of organisms (both sense and antisense gene therapy). The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The newly added limitation changes the scope of the claimed invention such that now the amended claims read upon antisense gene therapy. This raises the scope of enablement issue. The application as filed is enabled for performing in vitro homologous recombination in cells, but the application as filed is not enabled for in vivo gene therapy (sense or antisense) of diseased organisms. Hence 112 1st par. written description scope of enablement rejection that follows is being made.

The test of enablement is whether one reasonably skilled in the art could make or use the invention from the disclosures in the patent coupled with information known in the art without undue experimentation.

There are many factors to be considered based on the content of the disclosure when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue." In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

These factors include, but are not limited to:

(A) The breadth of the claims

The claims are drawn to homologous recombination in in vitro (cells) as well as in vivo organism's homologous recombination in diseased organisms. While there is support in the specification for performing in vitro recombination, the specification does not provide guidance how to perform the in vivo gene therapy methods. The in vivo invention (gene therapy using sense or antisense strands to perform homologous recombination in organisms) is a class of invention which the CAFC has characterized as "the unpredictable arts such as chemistry and biology." Mycogen Plant Sci;, Inc. v. Monsanto Co., 243 F.3d 1316, 1330 (fed. Cir. 2001)

(B) The nature of the invention

The invention is in area of biotechnology.

(C) The state of the prior art

The prior art provides many examples indicating in vitro homologous recombination can be performed successfully in vitro cultured cells. However despite a great deal of research time and money spent worldwide, to develop protocols and conditions, that can be routinely applied to successfully perform gene therapy (in vivo homologous recombination in diseased organisms); the current state of the art of gene therapy techniques is unpredictable.

(D) The level of one of ordinary skill

The level of one of ordinary skill in the biomedical art is very high, average researcher is PhD with several years of postdoctoral experience or MD/PhD with both clinical as well as research experience or a highly trained clinician.

(E) The level of predictability in the art

It remains that scientists, even today, have not yet overcome the various factors that are known to complicate the gene therapy art. Nyberg et al. (Molecular Therapy, 2004) provides a summary of the scientific, clinical, ethical, and social challenges associated with the long-term effects of gene therapy techniques in humans. Nyberg et al., summarized the scientific issues associated with human gene transfer, particularly the discussion focused on the potential for long-term risks, including the persistence of vector sequences, integration of the vector into host genomic DNA, and transgene-specific effects. According to Dr. Carolyn Wilson, in the Nyberg et al. article, long-term risks due to vector persistence would be most strongly affected by whether the vector integrates, potentially leading to dysregulated gene expression. The potential for tumorgenesis associated with dysregulated gene expression as a result of the genomic

integration of vector sequences, was also discussed. Moreover, Dr. Wilson also discussed transgene-specific effects associated with human gene transfer, such as tumorgenic effects of the transgene itself, the induction of autoimmune disease in genetic disorders, adverse effects caused by constitutive transgene expression for a normally tightly regulated gene, and the potential for complications when the transgene is expressed in cell types where the endogenous gene is not normally expressed (e.g., a liver-specific gene expressed in blood cell). Dr. Carter, in the Nyberg et al. article, described an adeno-associated vector and plasmids that have little potential for integration, and concluded that the vectors pose little or no long-term risk in study subjects, however his are not supported by any data wherein the integrational effects of the these vectors were studied in long-term experiments. It remains that the current state of the art of gene therapy techniques is unpredictable.

(F) The amount of direction provided by the inventor

Inventor has provided good guidance how to practice the in vitro recombination protocols but has not provided any guidance that is necessary to perform the in vivo homologous recombination protocols involving whole organisms in clinical settings.

(G) The existence of working examples

The specification does not provide a single working example that can serve as a guideline for one of ordinary skill as to how to practice the claimed invention with respect to the in vivo (sense and antisense gene therapy) homologous recombination of diseased organisms.

(H) The quantity of experimentation needed to make or use the invention

The quantity of experimentation to successfully perform in vivo homologous recombination in whole organisms to perform sense or antisense gene therapy protocols requires much time, effort, and money. One of ordinary skill would have to experimentally determine all the necessary parameters/conditions assays for monitoring the efficacy of different interventions being performed in vivo on the specific diseased organism. This means model test organisms would have to be developed for each disease condition sought to be corrected etc.

In conclusion based on the above considerations Examiner reaches the conclusion that one of ordinary skill will have to perform undue experimentation that will require both much time and money without having a reasonable expectation of success that the claimed method namely in vivo (gene therapy) homologous recombination protocol of whole organism will actually be successful. Hence the disclosure is not enabling for the in vivo gene therapy related claims.

Claim Rejections - 35 USC § 103

6. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

7. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation

under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

8. Claims 12-16 are rejected under 35 U.S.C. 103(a) as being unpatentable over Grunert et al. (US pat. 6,010,908 issued Jan 4, 2000) in view of Moriya (1993) Proc. Natl. Acad. Sci. USA vol. 90 pp1122-1126 and Marron et al. (2000) Diabetes vol. 49: pp 492-499.

Regarding claim 12, Grunert et al. teach a base conversion method of a DNA sequence (see title where term gene therapy is used to teach a base conversion method of a DNA sequence),

which is a method of converting one or more bases in a target DNA sequence in a cell (see col. 4 lines 35-37 where small fragment homologous replacement (SFHR) of mutated gene sequences in vivo and vitro are taught. By teaching targeted SFHR of the mutated cystic fibrosis (CF) gene (see col. 4 lines 43-44) in a subjects's target cells, Grunert et al. teach a method of converting one or more bases in a target DNA sequence in a cell)

characterized by introducing a single-stranded DNA fragment (see col. 54 lines 34-35 where 491 nucleotide single stranded DNA (ssDNA) is taught. See col. 54 lines 55-57 where electroporation is taught as a method to introduce the 491 nt. ssDNA into cells.

having 300 to 3,000 bases (by teaching 491 base ssDNA, Grunert et al. teach 300 to 3,000 bases)

is homologous with the target DNA sequence, and contains the base(s) to be converted, into a cell (the 491 base fragment was derived from a 860 bp fragment contained in CFTR exon 10, as well as 5' and 3' intron sequence. See col. 54 lines 10-20) thus the 491 base ssDNA is homologous with the target (CF) DNA sequence.

Regarding claim 12, Grunert et al. teach the formation of the ssDNA by denaturation of 491 bp DNA fragment obtained by PCR (see col. 54 lines 39-50).;

wherein the single-stranded DNA fragment is homologous with either a sense strand or an antisense strand of the target DNA. (Since Grunert et al. teach the formation of the ssDNA by denaturation of 491 bp DNA fragment obtained by PCR therefore they inherently teach wherein the single-stranded DNA fragment is homologous with either a sense strand or an antisense strand of the target DNA as the denatured PCR fragment will contain the single-stranded DNA fragment that make up the + and - strand so by definition it will comprise strand is homologous with either a sense strand or an antisense strand of the target DNA.

Regarding claim 14, Grunert et al. teach, wherein the single-stranded DNA fragment is homologous with a sense strand of the target DNA sequence (see col. 54 line 35 where 491 nt ss DNA fragment is used for homologous replacement. Since the ss DNA was made by denaturing the ds DNA therefore the mixture of ss DNA fragments contains both the sense and the antisense strand of the target DNA sequence.

Therefore Grunert et al. teach, wherein the single-stranded DNA fragment is homologous with a sense strand of the target DNA sequence.

Regarding claim 15, Grunert et al. teach wherein the target DNA sequence in the cell is a DNA sequence causing a disease due to the one or more bases (see col. 53 example 18 where target DNA taught is mutant CFTR which causes cystic fibrosis due to mutant CFTR gene. Thus teaching the target DNA sequence in the cell is a DNA sequence causing a disease due to the one or more bases).

Regarding claim 15, Grunert et al. teach, wherein one or more bases in a target DNA sequence in a cell of an organism are converted (See col. 56 lines 1-25 where homologous DNA replacement was confirmed by allele-specific southern hybridization).

Regarding claim 12, Grunert et al. do not teach single-stranded DNA fragment is prepared by cleavage from a single-stranded circular DNA,

Regarding claim 12, Moriya teaches single-stranded DNA fragment is prepared by cleavage from a single-stranded circular DNA (see page 1123 par. 1 where ss pMS2 phagemids (single stranded circular DNAs) are taught and enzyme EcoRV sal I are taught to cleave ss pMS2. Thus Moriya teaches single-stranded DNA fragment is prepared by cleavage from a single-stranded circular DNA.

Regarding claim 13, Moriya teaches wherein the single-stranded circular DNA is a phagemid DNA (ss pMS2 is taught as a phagemid see above).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to practice the method of Moriya in the method of Grunert

et al. The motivation to do so is provided to one of ordinary skill in the art both by teachings of Moriya as well as knowledge of the art itself.

Moriya states "It is concluded that a single—stranded shuttle vector, utilized in conjunction with a site-specific approach, can be used to investigate translesional events in mammalian cells and in bacteria". (see page 1122 end of abstract).

Thus by above teaching of Moriya one of ordinary skill knows that phagemids (ss DNA vector pMS2 derived from the pSVK3 backbone sold by Pharmacia—see page 1122 materials and method section) taught by Moriya can be used to generate single stranded DNA fragments that can be introduced into mammalian cells.

Grunert et al. teach a method using which they were able to convert one or more bases of CFTR mutated gene in a cell to alleviate the symptoms of CFTR, one of ordinary skill can envisage applying the method to various other diseases that are caused by known genetic lesions.

One of ordinary skill knows that if they want to target the coding sequence for human gene intended for alteration then they need to introduce a single stranded DNA that is homologous with a sense strand of the target DNA sequence.

100 kb Phagemid artificial chromosomes (Marron et al. 2000) that contain Type I Diabetes susceptibility gene (IDDM12) was taught to one of ordinary skill by prior art at the time of the invention. Hence one ordinary skill would be motivated to subclone the (IDDM12) gene from the above 100 kb construct into phagemid vectors taught by Moriya such that the ssDNA produced is homologous with a sense strand of the target (IDDM12) gene. By using the phagemid shuttle vectors not only are they able to

propagate and amplify these clones in bacteria, but also obtain a pure single stranded DNA substrate containing the desired DNA strand without requiring additional steps of PCR amplification followed by denaturation where only 50% of the strands will have the desired sequence. The resulting method is both faster and cleaner method. In addition such a method will produce 100 % ssDNA of desired sequence. These ssDNA circular DNA, can be cleaved by restriction enzymes to provide fragments, which can be used in the gene therapy protocols.

Conclusion

9. All claims under consideration 12-16 are rejected over prior art.

10. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to SUCHIRA PANDE whose telephone number is (571)272-9052. The examiner can normally be reached on 8:30 am -5:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on 571-272-0782. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Kenneth R Horlick/
Primary Examiner, Art Unit 1637

Suchira Pande
Examiner
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